Epitomes

Important Advances in Clinical Medicine

Family and General Practice

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The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in family and general practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in family and general practice that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Family and General Practice of the California Medical Association, and the summaries were prepared under the direction of Drs Sonander and Rai and the Panel.

Advances in Dementia Management

DEMENTIA IS A SYNDROME of progressive cognitive and functional decline that affects 5–10% of the US population aged 65 and older. Its incidence doubles every 5 years after age 65.

Clinicians often underestimate the amount of impairment that older patients experience in daily living. Only about one half of patients with dementia are identified by primary care physicians using the routine history and physical examinations. Early recognition of dementia may allow for treatment of reversible causes, amelioration of partially reversible causes, and delay of functional disability for some irreversible causes of dementia. Approximately 10–15% of cognitive impairment in older adults is due to treatable conditions such as hypothyroidism and drug toxicity. Early identification of patients with dementia allows the patient and family to plan for future long-term-care services, and to take the opportunity to participate in trials of new, potentially helpful therapies. Unrecognized dementia may result in inappropriate use of emergency services and unneeded patient/family discomfort.

The Agency for Health Care Policy Research (AHCPR) recently issued clinical practice guidelines to assist health care professionals in the early and accurate identification of Alzheimer's disease, the most common cause of dementia. Because dementia is often misdiagnosed or unrecognized in its early stages, the guidelines identify early symptoms and signs of dementia, guiding early assessment. Certain symptoms, such as problems with spatial ability and orientation or difficulties in learning, language, and handling complex tasks, distinguish early-stage dementia from normal aging and from other syndromes that affect cognition such as depression or delirium. These triggers prompt early assessment such as focused history, physical, functional, and mental status assessment. Using these decision support guidelines, primary care clinicians may identify the cause of dementia with greater accuracy.

Specific identification of Alzheimer's disease allows early treatment with newer agents that may better control behavioral signs and symptoms, improve cognitive function, and slow disease progression. Patients suffering from dementia commonly suffer from behavioral symptoms such as depression, anxiety, psychosis, aggression, agitation, and apathy. More effective medications are now available for the treatment of these conditions resulting from expanded Medicaid formulary inclusion of existing effective agents (such as serotonin reuptake inhibitors, SSRIs), the recognition that antiepileptic drugs have utility in behavior management (carbamazepine, valproic acid), and the introduction of newer psychotropics with fewer side effects (respiradol, olanzepine).

Therapies thought to enhance cognitive function in Alzheimer's disease by restoring functional deficits in neurotransmission, increasing cholinergic transmission, are available. Two cholinesterase inhibitors (tetrahydroaminoacridine and donepezil) show promise, both of which have been approved by the Food and Drug Administration. The use of each has demonstrated significant improvements in cognition and function, delaying suffering and costly use of long-term-care resources. There is modest evidence to support the benefit of selegiline, a monoamine oxidase inhibitor, and Vitamin E, which have been shown to cause mild improvement in cognitive function and behavior.

It is crucial that clinicians carefully evaluate patients with suspected dementia, obtaining information from informants, perform appropriate laboratory and imaging tests, and render a specific dementia diagnosis. Patients

should then be monitored for intercurrent medical problems, which frequently present as a worsening of dementia symptoms. Such problems should be treated, and dementia symptoms monitored. Improving sensory input can result in diminishing dementia symptoms and improved function. Environmental modification such as improving lighting, decreasing noise levels, and controlling wandering while promoting environmental exploration may lead to improved function. Clinicians can ease exhaustion and conflicts by teaching patients, families, and caregivers about available community resources that can help with coping with the illness and planning long-term-care services. These include Area Agency on Aging (in-home and community services; nutrition), Alzheimer's Disease Centers (clinical services; research and education), and the Alzheimer's Association (education; support groups; adult day care; respite).

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Treatment for Human Immunodeficiency Virus (HIV) Infection

AS RECENTLY AS 1993 and the International AIDS Conference in Berlin, the future of HIV antiretroviral therapy had darkened to a depressing gray. The Concorde Study questioned the long-term value of zidovudine (AZT) monotherapy for asymptomatic individuals, while other studies involving people with advanced disease found minimal benefit from switching to, or adding another, antiretroviral therapy. In the last 4 years, however, antiretroviral therapy has experienced a revival. Plasma HIV RNA testing allows close monitoring of HIV therapy, which has become more effective with the development of a more potent class of antiretrovirals, protease inhibitors. After years of being in desperately short supply, hope can again be found within offices of physicians treating HIV disease.

Multiple studies have demonstrated the predictive value of plasma HIV RNA levels, commonly referred to as "viral loads." This testing measures the amount of ongoing HIV replication, which correlates with the rate of CD4 cell destruction. In contrast to CD4 testing—a static measure of immune system damage—this test is a dynamic marker predicting the risk of future damage and, therefore, disease progression. Perhaps the most valuable role of HIV RNA testing, when used along with CD4 testing, is to help individualize the starting and changing of a patient's antiretroviral regimen.

Recent developments in antiretroviral drugs have also been dramatic. As of the Berlin Conference, only four drugs (zidovudine, didanosine, zalcitabine, and stavudine) were readily available, and all four were in the same class (nucleoside reverse transcriptase inhibitors). At present, 11 antiretrovirals have been approved by the Food and Drug Administration, including a new nucleoside (lamivudine) and six drugs in two new categories. Saquinavir, ritonavir, indinavir, and nelfinavir are protease inhibitors, which act on protease, another enzyme essential to the HIV life cycle. Nevirapine and delavirdine are non-nucleoside reverse transcriptase inhibitors (NNRTIs), which inhibit reverse transcriptase, but have a different chemical structure than nucleosides. Protease inhibitors are potent, having a monotherapy capacity to reduce viral load by 1- to 2-log; other drugs typically yield only a 0.5- to 1-log reduction.

Generally, a protease inhibitor is used in combination with at least two other drugs—a mode of treatment dubbed "highly active antiretroviral therapy" (HAART). The goal of HAART is to reduce plasma HIV RNA assays to below a detectable level (around 100–500 copies/ml, depending on technology used). The short-term benefit of HAART has been well demonstrated, perhaps most dramatically in a ritonavir study that found a survival advantage for people with advanced disease randomized to receive ritonavir along with whatever drugs they were receiving. Pending further research, long-term clinical benefit remains largely theoretical. Two advantages of prolonged suppression of HIV are anticipated. A dramatic reduction in the rate of CD4 cell destruction should lead to a marked slowing in HIV progression, and the synergistic activity of a multiple-drug regimen should significantly delay the development of drug resistance.

Now more than ever, drug resistance is a major concern. At one extreme of antiretroviral potency—the absence of any drug therapy—HIV will not experience the selective pressure that leads to resistance. At the other extreme—a highly potent therapy that suppresses HIV to undetectable levels—mutation to a resistant strain is dramatically slowed. The risk of resistance is greatest when potency is intermediate, when a regimen uses weaker drugs or is prescribed in insufficient doses, or because a person intermittently misses doses, leading to prolonged troughs in drug serum levels.

To address this last concern, the primary care physician can foster patient compliance in several ways: 1) evaluating each person's ability to adhere to a given regimen; 2) pretreating substance abuse and social instability; 3) educating about a new regimen (including a detailed schedule of dosing including food and water restrictions, and information about drug interactions and toxicities); and 4) suggesting strategies that will support adherence (a pillbox, a note on the bathroom mirror or refrigerator, an alarm-watch, extra supplies of medications at places fre-